UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,345	02/15/2006	Graeme Semple	22578-005US1 079.US2.PCT	6159

26204 7590 05/31/2011

FISH & RICHARDSON P.C.
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
CHUNG, SUSANNAH LEE	
ART UNIT	**PAPER NUMBER**
1626	

NOTIFICATION DATE	DELIVERY MODE
05/31/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/535,345
Filing Date: February 15, 2006
Appellant(s): SEMPLE ET AL.

Susanne Goodson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 30th, 2011 appealing from the Office action mailed June 1st, 2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 65-67 are pending and rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(**8) Evidence Relied Upon**

Sparatore, et al., *[4-(2H-1,2,3-Benzotriazol-2-yl)phenoxy]alkanoic Acids as Agonists of PPARs,* Chem & Biodiver., Vol. 3, 2006, 385-395, especially page 390, approx. lines 10-15.)

Semple, et al., *1-Alkyl-benzotriazole-5-carboxylic Acids Are Highly Selective Agonists of the Human Orphan G-Protein-Coupled Receptor GPR109b*, J. Med. Chem. 2006, 49, 1227-1230, especially page 1229, column 2, approx. lines 28-31.

James Wilson, *Enablement for Derivatives of Compositions of Matter,* Biotechnology, Chemical & Pharmaceutical Customer Partnership Meeting, U.S. Patent and Trademarks Office, March 12, 2008, 1-27.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

I. Claim 67 is rejected under 35 U.S.C. § 112, ¶ 1, as being non-enabled with respect to the recited method.

II. Claims 65-67 are rejected under 35 U.S.C. § 112, ¶ 1, as being non-enabled with respect to the terms “solvate” and "hydrate.”

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 67 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method of lowering free fatty acids in an individual comprising administering to said individual a therapeutically-effective amount of 3-(1-H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole, or a pharmaceutically acceptable salt, solvate or hydrate thereof. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with this claim.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to Claim 67 of the present invention below:

(1) The Nature of the Invention

The nature of the invention is drawn to a method of using a therapeutically-effective amount of 3-(1-H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole, or a pharmaceutically acceptable salt, solvate or hydrate thereof for lowering free fatty acids in an individual.

(2) The Breadth of the claims

Claim 67 will be given its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, the breadth of the claim includes not only the use of the compound 3-(1-H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole in lowering free fatty acids, but the tens of thousands of salts, solvates, and hydrates of the compound 3-(1-H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole.

Also, the breadth and scope of the term "lowering free fatty acids" cannot be ascertained. It is acknowledged that the mechanism of action of lowering free fatty acids in an individual is known in the art; however, in a method claim where terms are given their broadest reasonable interpretation it is not enough to claim a mechanism of action that could be interpreted to encompass tens of thousands of disorders that are associated with that mechanism of action. Specifically, one of ordinary skill in the art when hearing the term "lowering free fatty acids" would automatically think of the tens of thousands of metabolic disorders, such as dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity and type 2 diabetes, wherein "lowering free fatty

acids" is associated. However, the instant specification does not address all of the potential metabolic disorders encompassed by the term "lowering free fatty acids" and whether the compound 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole will be able to lower free fatty acids in all individuals with all of the different types of disorders. It is well known in the art that the patient population can be unpredictable and has many different factors known and unknown that could affect the ability of the compound to lower free fatty acids in a individual in general.

(3) The state of the prior art

The state of the prior art at the time this application was filed indicates that specific compounds, such as benzotriazole compounds, can lower free fatty acids in an individual to treat specific disorders. The prior art is silent on the use of the instantly claimed compound and the instantly claimed class of compounds, i.e. tetrazoles, to lower free fatty acids in an individual. Further, the prior art teaches that lowering free fatty acids is always linked to the treatment of a specific disorder.

In a journal article by Sparatore, [4-(2H-1,2,3-benzotriazol-2-yl)phenoxy]alkanoic acids were synthesized and tested as agonists of Peroxisome Proliferator-Activated Receptor (PPAR) for use in the treatment of dyslipidemic type-2 diabetes or dyslipidemia without diabetes. (See Sparatore, et al., Chem. & Biodiversity, Vol. 3, 2006, 385-395, especially page 390, approx. lines 10-15.)

In a journal article by Semple, the use of benzotriazole compounds as selective agonists of the Human Orphan G-Protein-Coupled Receptor GPR109b to treat

dyslipidemia and atherosclerosis is taught. (See Semple, et al., J. Med. Chem. 2006, 49, 1227-1230, especially page 1229, column 2, approx. lines 28-31.)

With respect to Appellant's claim to the use of tetrazole agonists of the nicotinic acid receptor RUP25 in lowering free fatty acids in an individual, the state of the art at the time of filing does not support its use in lowering free fatty acids in an individual for the treatment of a disorder.

(4) The relative skill of those in the art

The level of skill in the art would be high. The artisans synthesizing Appellant's compound and applying the method steps would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level (at least a bachelor's degree) and/or skill in the art, as well as several years of professional experience.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether the compound of the present invention could be reliably and predictably extrapolated to all individuals or patients in need of lowering of free fatty acids. It is well known in the art that individuals are

complex and vary greatly and that one compound could not possibly have the same mechanism of action, i.e. lowering free fatty acids, in 100% of all individuals even where the patient population is known, i.e. patients requiring treatment from dyslipidemia. Therefore, there is no predictability, even in view of the high level of skill in the art to claim that a compound can lower free fatty acids in all individuals without knowing what the patient population is.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses that the instantly claimed compounds can modulate the activity of the RUP25 receptor. See instant specification page 32. Appellants state that some embodiments of the present invention relate to methods of treatment of metabolic-related disorders, such as dyslipidemia and atherosclerosis. See instant specification page 32. Appellants provide specific biological data on pages 48-57, Examples 1-8. Of the examples, Example 8 is relevant to the method of lowering free fatty acids. Example 8 discloses a non-esterified free-fatty acid (NEFA) assay that was done on serum derived from live, freely moving rats.

The instant specification is mainly devoted to the chemical synthesis of the various tetrazole and pyrazole compounds. One skilled in the art would not be able to use the data provided in the instant specification to lower free fatty acids in an individual. The murine or rat model for lowering free fatty acids is acknowledged, but it is cursory and generic and a skilled artisan would not be able to draw any useful information from the description provided in Example 8 of page 57 of the instant specification. The example fails to discuss the specific compounds that were tested, the

test conditions and the specific binding capability of the compounds. The instantly claimed compound is a tetrazole compound; however, the instant specification discloses pyrazole and other classes of compounds. Therefore, absent specific data about which compounds were tested and the actual test conditions, the description provided in Example 8 would not provide any useful guidance to a skilled artisan.

(7) The presence or absence of working examples

The instant specification does not provide working examples. The specification discloses the general role of the compounds of the present invention as RUP25 agonists on pages 32-34 and 48-57 of the instant specification, but the data provided does not show how the instantly claimed compounds are RUP25 agonists or how the instantly claimed compounds act to treat a disorder.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role of the instantly claimed compound in lowering free fatty acids in an individual, it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which patients with which diseases would benefit from the claimed compound with a reasonable expectation of success. Therefore, claim 67 is not enabled.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds, compositions and salts of 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole, does not reasonably provide enablement for solvates or hydrates of this compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims recite specific compounds, and the salts, solvates and hydrates of said compounds. However, the specification fails to teach the preparation of solvates or hydrates. Therefore, the specification is not adequately enabled for solvates and hydrates.

Identifying a solvate requires knowledge of properties of the solvents and solutes of the instant compounds and nothing short of extensive testing (none identified) would be needed to determine if additional derivatives exist thus, such a scope as literally claimed herein is not enabled.

The examples presented all fail to produce a solvate or hydrate. These cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ 2d 1190, "the specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However…there is no evidence that such compounds exist…the examples of the `881 patent do not produce the postulated compounds…there is…no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates or hydrates of the instantly claimed compounds exist. If they did,

they would have been formed. Hence, applications must show that solvates and hydrates can be made, or limit the claims accordingly by deleting the terms solvates and hydrates.

It is not the norm that one can predict with any accuracy a particular solvate form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing in vivo. The specification provides no guidance as to what types are suitable for the instantly claimed compounds.

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented (by the inventor);
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary (to make and/or use the invention).

The eight Wands factors are applied to Claims 65-67 of the present invention below:

(1) The Nature of the Invention

The nature of the invention is drawn to the chemical synthesis of salts, solvates and hydrates of the compound 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole.

(2) The Breadth of the claims

The breadth of the claims encompasses salts, solvates and hydrates of the compound 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, the breadth of the claims includes the tens of thousands of forms encompassed by the terms salts, solvates and hydrates.

(3) The state of the prior art

The state of the art recognizes that the formation, composition and therapeutic activity of solvates, hydrates and polymorphs is unpredictable. The Federal Circuit (in SmithKline Beecham Corp. v. Apotex Corp., 74 USPQ2d 1398, 1409 (Fed.Cir. 2005)) has recognized solvates and hydrates, i.e. solvates where the solvent is water, as examples of polymorphs or pseudopolymorphs:

"Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon).... [P]seudopolymorphs are often loosely called polymorphs...

Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a *solvate*, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.

While the Federal Circuit addresses the fact that particular physical properties of hydrates, solvates and polymorphs can be different from the parent compound, the state of the prior art also recognizes that pharmaceutical properties, such as dissolution (which affects a particular compound's ability to elicit a desired biological response), can also be significantly different in hydrates, solvates and polymorphs compared to the parent compound.

(4) The relative skill of those in the art

The level of skill in the art would be high. The artisans synthesizing Appellant's hydrates, solvates and pharmaceutical compositions thereof, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level (at least a B.S. degree) and/or skill in the art, as well as several years of professional experience.

(5) The predictability or unpredictability of the art

The predictability of the art with regard to salts is known, but the preparation of solvates and hydrates are compound specific. In addition, the extremely large scope of potential solvates and hydrates that could be produced renders the prior art unpredictable for making or using products as claimed on such a grand scale.

As mentioned in section (3), there is a large degree of uncertainty in predicting the properties of a hydrate, solvate or polymorph given only the properties of the parent compound. There is no predictability in determining that a hydrate, solvate or polymorph will possess the same beneficial properties that make a given compound a drug candidate or similarly that a hydrate, solvate or polymorph will not possess the undesired properties that make a given compound unsuitable for pharmaceutical use. More importantly, there is a severe lack of predictability in determining whether a given compound will even form a solvate or hydrate and if so, whether multiple polymorphic forms can exist.

(6) The amount of direction or guidance presented (by the inventor)

The application is negligent regarding direction with respect to making and using solvates and hydrates. The terms solvates and hydrates are not defined in the specification and therefore can encompass both solution-phase and isolatable solvates. The specification merely mentions the Appellant's intention to include solvates and hydrates, without teaching the preparation thereof. There is no guidance in the specification drawn to the solvates and hydrates of the instantly claimed compounds. In addition, the specification provides no guidance as to what type(s) of solvates are suitable for the instantly claimed compounds.

(7) The presence or absence of working examples

The specification has no working examples of solvates or hydrates of the instantly claimed compounds. While the claims recite solvate and hydrates, no working examples are provided to show their formation.

Solvates and hydrates cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ 2d 1190, "the specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However…there is no evidence that such compounds exist…the examples of the `881 patent do not produce the postulated compounds…there is…no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates or hydrates of the instantly claimed compounds exist. If they did, they would have been formed. Hence, applications must show that solvates and hydrates can be made, or limit the claims accordingly by deleting the terms solvates and hydrates.

(8) The quantity of experimentation necessary (to make and/or use the invention)

The quantity of experimentation is undue given the state of the art and lack of predictability discussed in sections (3) and (5), undue experimentation is needed to practice the full scope of Appellant's instant invention especially in view of the lack of direction discussed in sections (6) and (7). Identifying a solvate requires knowledge of the properties of the solvents and solutes and their reactions and/or transformation, nothing short of extensive testing (none identified) would be needed to determine if additional derivatives exist and thus, such as scope as literally claimed herein is non-enabled.

(10) Response to Argument

Appellant has traversed the rejection of claim 65 under 35 U.S.C. §112, ¶ 1, for lacking enablement for a method of lowering free fatty acids in an individual comprising administering to said individual a therapeutically-effective amount of 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole. Examiner respectfully disagrees that the instant application enables one of ordinary skill in the art to use the compound 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole to lower free fatty acids in an individual. As a general rule, enablement must be commensurate with the scope of claim language. MPEP 2164.08 states, "the Federal Circuit has repeatedly held that 'the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.'" In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." Similar "make and use the full scope of the invention without undue experimentation" language was repeated as recently as 2005 in Warner-Lambert Co. v. Teva Pharmaceuticals USA Inc., 75 USPQ2d 1865. The instant application does not teach one of ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation. The claimed invention is directed to lowering free fatty acids in an individual comprising administering a therapeutically effective amount of 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole. As will be discussed, no where in the instant application is support found for lowering free fatty acids in an individual comprising administering a therapeutically effective amount of 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole.

Appellant has traversed the rejection of claims 65-67 under 35 U.S.C. §112, ¶ 1, for lacking enablement for solvates and hydrates of 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole. Examiner respectfully disagrees that the claims are enabled for the solvates and hydrates of the compound 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole. As a general rule, there is a heightened enablement requirement for chemical inventions. Specially, the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The instant application does not provide guidance or direction on the solvates and hydrates of the compound 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole. As will be discussed, no where in the instant application is support found for making solvates and hydrates of the compound 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole.

Appellant argues that the initial burden of enablement is on the Office and that the burden of enablement has not been met. Examiner agrees that the initial burden is on the Office, but respectfully disagrees that the Office's burden has not been met. See section (9) of the instant Examiners Answer outlining the enablement rejections, which were made in the office actions dated 6/24/08, 3/18/09, 10/19/09, and 6/1/10. Clearly, the Office's burden has been met. MPEP 2164.01(a) states, "a conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, ***at the time the application was filed***, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without

undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." As will be discussed, support for the method of lowering free fatty acids in an individual and for the terms solvates and hydrates are not found in the application as originally filed. Applicants have provided references post-filing date, but a conclusion of lack of enablement is based on the evidence regarding each of the *Wands* factors at the time of filing. Based on the application as filed, the instant claims 65-67 are not enabled.

I. The method of claim 67 is not enabled

The *Wands* factors are addressed.

(1) Nature of the Invention

The claim recites a method of lowering free fatty acids in an individual by administering the compound 3-(1H-tetrazol-5-yl)-1,4,5,6-tetrahydrocyclopentapyrazole, also known as MK-0354, or a pharmaceutically acceptable salt, solvate or hydrate thereof. Appellants cite the Semple and Lai journal articles, which were published in 2008, post-filing date. Based on these two references, Appellants state that the invention works in humans as demonstrated in the specification and are "at a loss to understand how an enablement rejection can be maintained after recognizing this fact." Appeal Brief page 4 of 26.

According to the MPEP, claims must be enabled at the time of filing. MPEP 2164.01(a) states, "a conclusion of lack of enablement means that, based on the

evidence regarding each of the above factors, the specification, ***at the time the application was filed***, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

However, for arguments sake, the post-filing references will be addressed because Appellants may be able to provide data showing that this was known at the timing of filing.

Even in view of the references, it is Examiner's position that the claim is not enabled. Appellants assert that this is a simple claim addressed to lowering free fatty acids and that they have demonstrated such in the Semple and Lai references. However, Examiner respectfully disagrees that "lowering free fatty acids" is a simple issue. Rather, "lowering free fatty acids" is quite complicated and due to the complex nature it is understandable why there are no small molecule claims drawn to "lowering free fatty acids" in U.S. patent claims thus far.

Appellants glance over the term "lowering free fatty acids" as well known in the art. However, it is asserted that a method drawn to "lowering free fatty acids" can mean a multitude of different methods to a skilled artisan. Office Actions dated 3/18/09, pages 2-3 and 10/19/09, pages 2-3. The issue with the instant application is that it does not discuss how the compound will lower free fatty acids.

The issue is one of claim construction. The scope and reach of the claim is unknown. The claim limitation "lowering free fatty acids" is broad and it is unpredictable what the scope of the claim is, which is why there are no U.S. patent claims drawn to

"lowering free fatty acids" using a small molecule. See office action dated 03/18/2009 (page 3) and 6/1/10 (page 3).

In particular, see the office action date 6/1/10, page 3, wherein the term "lowering free fatty acid" is discussed as the reason for the enablement rejection. The term is not enabled for several reasons (1) the specification does not specifically define what is meant by the term "lowering free fatty acids," (2) the specification does not indicate how much the fatty acid is "lowered," and (3) the specification does not discuss what the patient population is.

First, the specification does not define "lowering free fatty acids." Appellants may argue that it is self-explanatory because there is no definition in the specification, but claims are given their broadest reasonable interpretation. Where the specification provides no guidance for the term, it will be interpreted broadly. In the instant claims, the terms lowering and free fatty acids are all broad. For example, what is meant by the term "lowering?" Will the compound be lowering the concentration? Is it lowering the length of the fatty acid? Where is the lowering taking place? Also, what types of fatty acids are being targeted? Is it saturated or unsaturated?

Second, the specification does not disclose by how much the fatty acid is lowered. There is no biological data showing how much the compound lowers fatty acids. There is no biological data at all with regard to the instantly claimed compound. Any biological data in the specification is generic. The Semple and Lai references discuss the instantly claimed compound, however, the instant claim language fails to limit the scope of the claim to the data found in Semple and Lai.

Third, the patient population is unknown. Appellants do not appear to address this very important issue. Method claims must be carefully drafted so that the scope of the claim is clear and it does not reach through to other methods. The construction of the instant claim is too broad. The reason the patient population should be inserted into the claim, i.e. a method for treating dyslipidemia, is so that it is clear what the scope of use of the compound is. It is well known in the art that patient populations vary greatly and that a compound that works in one patient population may not work in another. The phase I clinical trial was done on healthy males. The claims are drawn to lowering free fatty acids in an individual. A healthy male individual is very different from an individual suffering from type 2 diabetes or some other metabolic disorder.

Also, with metabolic disorders there is a great degree of uncertainty because no two humans have the same amount of free fatty acids or even the same types of free fatty acids.

Furthermore, lowering free fatty acids is always associated with a disorder. Both the Semple and Lai articles address specific disorders, such as dyslipidemia, that are associated with the lowering of free fatty acids. Also, the instant specification discusses the consequences of decreasing plasma free fatty acids as two-fold. "First, it will ultimately lower LDL-cholesterol and raise HDL-cholesterol levels, independent risk factors, thereby reducing the risk of mortality due to cardiovascular incidence subsequent to atheroma formation. Second, it will provide an increase in insulin sensitivity in individuals with insulin resistance or type 2 diabetes." See instant specification page 2, ¶ 2. As can be seen from the specification and journal articles,

lowering free fatty acids is a complex issue and the scope of the claim should be limited to that for which there is support.

(2) State of the art; working examples; and the amount of guidance or direction provided

Appellants state that the state of the art, the working examples, and the amount of direction or guidance provided all weigh in favor of enablement because (1) nicotinic acid (niacin) was known at the time of filing, (2) the murine variant of the known GPR109A receptor was shown to mediate the metabolic effects of nicotinc acid, (3) nicotinic acid was known to bind to and agonize the GPR109A receptor, and (4) the claimed compound also binds to and agonizes the GPR109A receptor.

The instant specification does not provide any guidance or direction for lowering free fatty acids using 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole. Appellants rely on the state of the prior art, which generically discusses the GPR109A receptor and nicotinic acid and concludes that the instantly compound can lower free fatty acids in an individual. Examiner respectfully disagrees with Appellant's conclusion. It is Examiner's position that the use of generic journal articles to show that the instant compound can bind to and agonize the GPR109A receptor is not relevant when the compounds depicted in those journal articles are vastly different than the instantly claimed compounds. In the end, the specification is controlling because it provides the most specific data related to the instantly claimed compound. Appellants have not discussed the specification and have not pointed to anything in the instant application or

prior art that would support the use of 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole in lowering free fatty acids.

(3) The breadth of the claims

Appellants state that the scope of claim 67 is relatively narrow in scope and fully commensurate with enablement provided by the specification and the corroborating evidence of enablement summarized in Lai and Semple. First, the claimed method recites a single new chemical entity, rather a genus of such compounds. Second, the method is directed to treatment of a very specific type of dyslipidemia-high levels of free fatty acids (see specification, page 10, lines 14-17). Third, measurement of free fatty acid levels before or after administration of the claimed compound is a simple blood test measurement. See Sempie, supra, at 5107. Fourth, the claimed method has been definitively shown to work in humans. See Lai, supra, at 381.

Examiner respectfully disagrees that the scope of claim 67 is narrow. First, the amendment of the claim from a large genus to a single species is not at issue. The compound is not at issue. The enablement issue is with the term “lowering free fatty acids.” Applicants insist that any skilled person would known what this term means and what a method of lowering free fatty acids can do, but Examiner respectfully disagrees. See discussion in Section (1) above.

Second, Appellants state that "lowering free fatty acids" is describing a very specific type of dyslipidemia and that the scope is narrower. Examiner respectfully

disagrees with this conclusion. Lowering free fatty acids describes a multitude of different disorders in addition to dyslipidemia. Office action, 6/1/10, page 3.

Third, Appellants state that measuring free fatty acid levels is a simple blood test and should support the enablement of the claim. It is unclear how the simplicity of the blood test is relevant to the enablement of the claim. It is well known in the art that blood fatty acids are in different forms in different stages in the circulation. The test may be simple, but the data obtained from the test will vary depending on the individual and test conditions.

(4) The relative level of skill in the art

Examiner acknowledges the skill in the art is high.

(5) The predictability or unpredictability in the art

Appellants believe the Lai article to support the predictability of the art. However, Examiner respectfully disagrees. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The issue is whether the term "lowering free fatty acids" is predictable. It is asserted that this term is unpredictable and that the scope of the claims cannot be ascertained. See above and Office action, 3/18/09, pages 2-3 and Office action, 10/19/09, page3, and office action, 6/1/10, page 3-4.

(6) The quantity of experimentation necessary

Appellants assert that little experimentation is necessary to establish that the compound can lower free fatty acids. Examiner respectfully disagrees. The level of experimentation is great. As discussed above, the term “lowering free fatty acids” is broad and one of ordinary skill in the art would not know the following: (1) which fatty acids are being lowered; (2) how much are they being lowered; and (3) to what patient population can this compound be used. Appellants state that one would know it's a more narrow form of dyslipidemia; however, Examiner respectfully disagrees. Lowering free fatty acids in a method claim reaches through to other unclaimed disorders for which no data or evidence has been provided.

(7) Summary

As summarized above, in view of the *Wands* factors (2), (3), (5), and (6), instant claim 67 drawn to a method of lowering free fatty acids in an individual by administering the compound 3-(1H-tetrazol-5-yl)-1,4,5,6-tetrahydrocyclopentapyrazole, or a pharmaceutically acceptable salt, solvate or hydrate thereof is broad and would pose an undue burden on one of ordinary skill in the art as to how to use the invention.

Appellants state that this is a simple case wherein they are claiming one compound which lowers free fatty acids and the post-filing journals demonstrate this. The rejection is not based solely on whether the compound can or cannot lower free fatty acids, but the summation of the factors surrounding how far a claim drawn to

lowering free fatty acids can reach. Appellants state that this is a narrower claim because lowering free fatty acids describes a very specific type of dyslipidemia; however, "lowering free fatty acids" also encompasses a multitude of other metabolic disorders because all metabolic related disorders could potentially be treated by lowering free fatty acids. As discussed above, there is a lack of predictability as to which free fatty acids are encompassed by this claim and what is meant by lowering and the experimentation needed to identify these factors and the patient population that could benefit from this course of treatment is undue as discussed above.

The fundamental inquiry in the rejection is whether the specification and prior art teaches a person of skill how to make and use the invention, where Appellant has defined the invention, i.e. a method of lowering free fatty acids. The fundamental query relevant to enablement is whether the specification together with the knowledge in the prior art enables a person of skill to make and use the invention. As discussed above, the instant specification and prior art lacks any guidance.

For these reasons, the rejection of the instant claim under 35 U.S.C. §112, ¶ 1 as lacking enablement for a method of lowering free fatty acids is maintained.

II. The solvates and hydrates of claims 65-67 are not enabled

A. Prior decisions by the Board of Patent Appeals and Interferences (BPAI) do not support the enablement of solvates and hydrates in the instant application

Appellants cite two BPAI decisions on solvates and hydrates. See In re Liu, No. 2009-01 5302 [Bd. Pat. App. & Int. 9/17/10), and In re Germeyer, No. 2010-005038 (Bd. Pat. App. & Int. 12/3/2010). Examiner acknowledges these decisions; however, the facts of the instant application differ greatly from the facts of In re Liu and In re Germeyer. Thus, the holdings in these decisions do not apply to the facts of the instant application.

In *In re Liu*, the rejection of "solvate" was addressed. In this case, the specification specifically taught how to make a solvate. See *In re Liu*, No. 2009-015302, Decision, page 4. Compare this with the facts of the instant application. The instant specification does not teach how to make a solvate or hydrate in the specification or disclosure in general. Therefore, the Board's reversal of the solvate rejection in *In re Liu* does not apply to the instant application.

In *In re Germeyer*, the rejection of "hydrate" was addressed. In this case, the hydrate was an element of a steroid, i.e. step b, which was the second element of a composition, i.e. a propellent-free inhalable solution or suspension, comprising a compound and a steroid. See *In re Germeyer*, 2010-005038, Decision, Pages 2-3. On the other hand, the instant application is drawn to one specific compound, i.e. 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole, it's composition and method of using. The instant specification does not teach how to make or use the compound as a solvate or hydrate. Also, the hydrate of a steroid is very different from the hydrate of a compound. Therefore, the Board's reversal of the hydrate rejection in *In re Germeyer* does not apply to the instant application.

B. An analysis of the *Wands* factors indicates that the solvates and hydrates cannot be made without undue experimentation

The *Wands* factors are addressed.

(1) Nature of the Invention

The claims are drawn to a compound, 3-(1H-tetrazol-5-yl)-1,4,5,6-tetrahydrocyclopentapyrazole, and its pharmaceutically acceptable salt, solvate or hydrate thereof.

(2) State of the art; working examples; and the amount of guidance or direction provided

Appellants cite a statement in the office action, mailed 6/24/08, page 9, wherein it states "[i]t was known in the art at the time of this application that compounds can exist in salt, solvate and hydrate form." Appellants interpret this statement to be an admission on Examiner's part that the instant compounds can be in solvate and hydrate form; however, the statement was made under the heading – The state of the prior art. The state of the prior art is that compounds can exist in salt, solvate and hydrate form. Nowhere in the office action does it state that the instant compound can be made in solvate or hydrate form.

The issue is whether the instant specification and prior art together enables the instant compound to be in solvate or hydrate form. It is asserted by Examiner that

Appellants did not even envision a solvate or hydrate form of 3-(1H-tetrazol-5-yl)-1,4,5,6-tetrahydrocyclopentapyrazole at the time of filing. Unlike other applications that define the terms solvates and hydrates and give examples of how to make and use them in detail, the instant application does not provide any information regarding solvates or hydrates of 3-(1H-tetrazol-5-yl)-1,4,5,6-tetrahydrocyclopentapyrazole.

The application is negligent regarding direction with respect to making and using solvates and hydrates. The specification merely mentions the words solvates and hydrates, without defining it or teaching the preparation thereof. There is no guidance in the specification drawn to the solvates and hydrates of the instantly claimed compounds. In addition, the specification provides no guidance as to what type(s) of solvates and hydrates are suitable for the instantly claimed compound.

The specification has no working examples of solvates or hydrates of the instantly claimed compounds. While the claims recite solvate and hydrates, no working examples are provided to show their formation.

Identifying a solvate and hydrate form requires knowledge of the properties of the solvents and solutes and their reactions and/or transformation, nothing short of extensive testing (none identified) would be needed to determine if additional derivatives exist and thus, such as scope as literally claimed herein is non-enabled.

(3) The breadth of the claims

Appellants state that the claims are narrow in scope because only one compound is at issue. Appeal Brief, page 14 of 26. Once again, Appellants state that the claims

are drawn to one compound. The scope of the compound is not at issue for the instant enablement rejection. The enablement rejection is not made on the scope of the compound, but rather the scope of the terms solvates and hydrates.

The breadth of the terms solvates and hydrates are not enabled in the instant application because Appellants do not provide any definitions for the terms, or any methods of making, or methods of using, or working examples of possible solvates and hydrates of the compound. Therefore, the solvates and hydrates of the one compound in actuality encompass tens of thousands of different compounds.

(4) The relative level of skill in the art

Examiner acknowledges the skill in the art is high.

(5) The predictability or unpredictability in the art

The predictability of the art with regard to salts is known, but the preparation of solvates and hydrates are compound specific. In addition, the extremely large scope of potential solvates and hydrates that could be produced renders the prior art unpredictable for making or using products as claimed on such a grand scale.

The state of the art recognizes that the formation, composition and therapeutic activity of solvates, hydrates and polymorphs is unpredictable. The Federal Circuit (in SmithKline Beecham Corp. v. Apotex Corp., 74 USPQ2d 1398, 1409 (Fed.Cir. 2005)) has recognized solvates and hydrates as examples of polymorphs or pseudopolymorphs:

"Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon).... [P]seudopolymorphs are often loosely called polymorphs... Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a *solvate*, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.

While the Federal Circuit addresses the fact that particular physical properties of hydrates, solvates and polymorphs can be different from the parent compound, the state of the prior art also recognizes that pharmaceutical properties, such as dissolution (which affects a particular compound's ability to elicit a desired biological response), can also be significantly different in hydrates, solvates and polymorphs compared to the parent compound.

(6) The quantity of experimentation necessary

Appellants assert that little experimentation is necessary to establish that a compound can be a solvate or hydrate. Examiner respectfully disagrees. The level of experimentation is great.

Solvates and hydrates cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ 2d 1190, “the specification

purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However…there is no evidence that such compounds exist…the examples of the `881 patent do not produce the postulated compounds…there is…no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates or hydrates of the instantly claimed compounds exist. If they did, they would have been formed. Hence, applications must show that solvates and hydrates can be made, or limit the claims accordingly by deleting the terms solvates and hydrates.

The quantity of experimentation is undue given the state of the art and lack of predictability discussed above, undue experimentation is needed to practice the full scope of Appellant's instant invention especially in view of the lack of direction discussed above. Identifying a solvate and hydrate requires knowledge of the properties of the solvents and solutes and their reactions and/or transformation, nothing short of extensive testing (none identified) would be needed to determine if additional derivatives exist and thus, such as scope as literally claimed herein is non-enabled.

(7) Summary

The rejection is not based solely on the difference in properties but the summation of the factors surrounding the generation of solvates and hydrates. As discussed above, there is a lack of predictability as to whether 3-(1H-tetrazol-5-yl)-1,4,5,6-tetrahydrocyclopentapyrazole can even form a single usable solvate or hydrate

and the experimentation needed to identify which solvents and conditions are required to make them is undue as discussed above.

The fundamental inquiry in the rejection is whether the specification teaches a person of skill how to make and use the invention, where Appellant simply claims solvates and hydrates without supporting it. The fundamental query relevant to enablement is whether the specification together with the knowledge in the prior art enables a person of skill to make and use the invention. As discussed above, the instant specification lacks any guidance as to which compounds can form a solvate or a hydrate. Even if the compound can form a solvate or a hydrate, how many solvates and hydrates are formed, of those potential products that can be formed, what procedures should be used to generate them, and then which of those possess the appropriate properties to be useful in the instant pharmaceutical uses?

For these reasons, the rejection of the instant claims under §112, ¶ 1 as lacking enablement for solvates and hydrates is maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Susannah Chung/

Primary Examiner, Art Unit 1626

Conferees:

/Joseph K. McKane/

Supervisory Patent Examiner, Art Unit 1626

/James O. Wilson/

Supervisory Patent Examiner, Art Unit 1624